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CofC

Patent No.: 5,061,703 C1 Attorney Docket No.: 03269/0200721-US1

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Request for Certificate of Correction (2 pp.)
Certificate of Correction (1 p.)
Exhibit A: Amendment filed Aug 18, 2004 (3 pp.)
Exhibit B: Amendment filed May 9, 2005 (19 pp.)
Exhibit C: Amendment filed October 17, 2005 (4 pp.)
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Customer No.: 07278

Docket No.: 03269/0200721-US1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Letters Patent of: Joachim Bormann, et al.

Patent No: 5,061,703 C1

Patent Issued: October 29, 1991

Ex Parte Reexamination Control No.: 90/007,176

Ex Parte Reexamination Certificate Issued: November 7, 2006

For: ADAMANTANE DERIVATIVES IN THE PREVENTION AND TREATMENT OF CEREBRAL ISCHEMIA

REQUEST FOR CERTIFICATE OF CORRECTION
PURSUANT TO 37 CFR 1.322

Attention: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Upon reviewing the above-identified Ex Parte Reexamination Certificate, the Patentee noted the following Patent Office errors, which should be corrected:

At claim 1, line 56, "wherein" was added to this claim in the Amendment filed August 18, 2004 at pages 1-2 (copy enclosed as Exhibit A), and should therefore be italicized.

At claim 1, line 57, a comma was included between "R_4" and "and" in the Amendment filed August 18, 2004 at pages 1-2, and should therefore be added.

At claim 1, line 58, a comma (not a semi-colon) was included after "simultaneously" in the Amendment filed August 18, 2004 at pages 1-2, and should therefore be inserted in place of the semi-colon.

At claim 10, line 62, a comma was included between "disease" and "wherein" in the Amendment filed May 9, 2005 at page 4 (copy enclosed as Exhibit B), and should therefore be added.

At claim 18, line 64, the word "is" was used in the Amendment filed October 17, 2005 at page 2 (copy enclosed as Exhibit C), and should therefore be inserted in place of "in."

These errors were made by the U.S. Patent and Trademark Office (USPTO) and through no fault of the Patentee. This is clearly established by reference to the records of this reexamination proceeding in the USPTO. Accordingly, no fee is due.

Transmitted herewith is a proposed Certificate of Correction effecting such amendment. The Patentee respectfully solicits the granting of the requested Certificate of Correction.

Dated: November 30, 2006

Respectfully submitted,

By_____

S. Peter Ludwig
Registration No.: 25,351
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant

DEC 0 8 2006

PTO/SB/44 (04-05)
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U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.	:	5,061,703 C1
APPLICATION NO.	:	90/007,176
ISSUE DATE	:	November 7, 2006
INVENTOR(S)	:	Joachim Bormann et al.

It is certified that an error appears or errors appear in the *Ex Parte* Reexamination Certificate of the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 1, line 56: delete "wherein" and substitute --*wherein*--.

Claim 1, line 57: delete "R_4 *and*" and substitute --R_4, *and*--.

Claim 1, line 58: delete "*simultaneously;*" and substitute --*simultaneously,*--.

Claim 10, line 62: delete "disease *wherein*" and substitute --disease, *wherein*--.

Claim 18, line 64: delete "in" and substitute --is--.

MAILING ADDRESS OF SENDER:
S. Peter Ludwig
DARBY & DARBY P.C.
P.O. Box 5257
New York, NY 10150-5257

Express Mail Label No: EL983949838US Dated: 8/18/04

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Customer No.: 07278

Docket No.: 03269/0200721-US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: Joachim BORMANN, Markus GOLD, and Wolfgang SCHATTON

Patent No.: 5,061,703

Issue Date: October 29, 1991

Assignee: Merz Pharma GmbH & Co. KGaA

Title: ADAMANTANE DERIVATIVES IN THE PREVENTION AND TREATMENT OF CEREBRAL ISCHEMIA

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PROPOSED AMENDMENT PURSUANT TO 37 C.F.R. § 1.510(e)

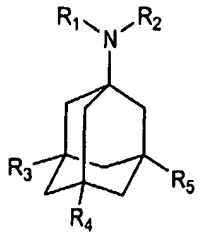
Sir:

In the event that reexamination of U.S. Patent No. 5,061,703 ("the '703 patent") is granted, please amend the claims of the '703 patent as follows pursuant to 37 C.F.R. § 1.510(e):

IN THE CLAIMS:

Pursuant to 37 C.F.R. §§ 1.530(d)-(j), please amend claim 1 as follows:

1. (Amended) A method for the prevention or treatment of cerebral ischemia comprising the step of administering, to a patient in need thereof, an effective amount of an adamantane derivative of the general formula



wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1-C_6 alkyl group[,]; and

wherein

R_1, R_2, R_3, R_4, and R_5 do not all represent hydrogen simultaneously,

or a pharmaceutically-acceptable salt thereof.

REMARKS

This amendment is submitted concurrently with a Request for Reexamination of the '703 patent pursuant to 35 U.S.C. § 302 and 37 C.F.R. § 1.510.

I. Status of Claims

Claims 1-3, 6, 8, and 10-13 are pending in this reexamination.

Claim 1 has been amended to include the proviso that R_1, R_2, R_3, R_4, and R_5 do not all represent hydrogen simultaneously in the claim 1 general formula.

II. Support For Claim Changes

Support for the amendment to claim 1 is found in the '703 patent specification at column 3, lines 18-20. No new matter has been added, and the scope of the claims has not been enlarged. *See In re Johnson*, 558 F.2d 1008, 1019 (CCPA 1977) (concluding that a claim excluding subject matter lost in an interference proceeding was adequately supported by the specification because the "specification, having described the whole, necessarily described the part remaining"); *In re Wertheim*, 541 F.2d 257, 263-66 (CCPA 1976) (holding that claim covering a broad range may be amended to exclude the prior art based on disclosed examples).

III. Purpose of Claim Amendment

The purpose of the amendment to claim 1 is to exclude 1-amino adamantane from the subject matter covered by the claim. The use of 1-amino adamantane is disclosed in JP '718.

IV. Conclusion

It is respectfully requested that a certificate of reexamination be granted and the above proposed amendment of claim 1 be considered in accordance with 37 C.F.R. § 1.510(e).

Dated: August 18, 2004

Respectfully submitted,

By _____
S. Peter Ludwig
Reg. No. 25,351
Attorney for Requester

Darby & Darby P.C.
Post Office Box 5257
New York, NY 10150-5257
212-527-7700

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Customer No.: 07278

Docket No.: 03269/0200721-US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Reexamination of: U.S. Patent No. 5,061,703
Of Joachim BORMANN, Markus GOLD, and Wolfgang SCHATTON

Control No: 90/007,176

Examiner: Kevin E. Weddington

Confirmation No.: 5288

Art Unit: 1614

Filed: August 18, 2004

Title: ADAMANTANE DERIVATIVES IN THE PREVENTION AND TREATMENT OF CEREBRAL ISCHEMIA

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT PURSUANT TO 37 C.F.R. § 1.530

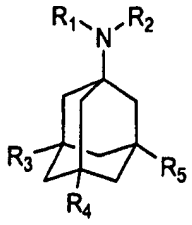
Sir:

In response to the Office Action mailed March 10, 2005, and pursuant to 37 C.F.R. §§ 1.530(d)-(j), please amend the claims of U.S. Patent No. 5,061,703 ("the '703 patent") as follows:

IN THE CLAIMS:

Please amend claim 1 as follows:

1. (Twice Amended) A method for the prevention or treatment of cerebral ischemia comprising the step of orally administering, to a patient diagnosed with Alzheimer's disease and in need thereof, an effective amount of an adamantane derivative of the general formula



wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1-C_6 alkyl group; and

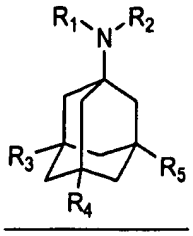
wherein

R_1, R_2, R_3, R_4, and R_5 do not all represent hydrogen simultaneously;

or a pharmaceutically-acceptable salt thereof.

Please add new claims 14-25 as follows:

14. (New) A method for the treatment of cerebral ischemia comprising orally administering to a patient diagnosed with Alzheimer's disease and in need of such treatment an effective amount of an adamantane derivative of the general formula



wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1-C_6 alkyl group; and

wherein

R_1, R_2, R_3, R_4, and R_5 do not all represent hydrogen simultaneously,

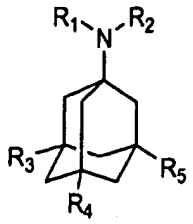
or a pharmaceutically-acceptable salt thereof.

15. (New) The method of claim 14, wherein said adamantane derivative is memantine.

16. (New) The method of claim 14, wherein said effective amount is from about 0.01 to 100 mg/kg.

17. (New) A method for the treatment of an imbalance of neuronal stimulation after Alzheimer's disease, comprising orally administering to a patient diagnosed with Alzheimer's

disease and in need of such treatment an effective amount of an adamantane derivative of the general formula



wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1-C_6 alkyl group; and

wherein

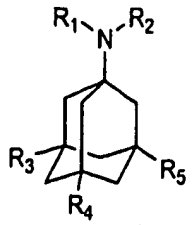
R_1, R_2, R_3, R_4, and R_5 do not all represent hydrogen simultaneously,

or a pharmaceutically-acceptable salt thereof.

18. (New) The method of claim 17, wherein said adamantane derivative is memantine.

19. (New) The method of claim 17, wherein said effective amount is from about 0.01 to 100 mg/kg.

20. (New) A method for blocking an excessive influx of calcium through NMDA receptor channels in a patient diagnosed with Alzheimer's disease and in need of such treatment, comprising orally administering to said patient an effective amount of an adamantane derivative of the general formula



wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1-C_6 alkyl group; and

wherein

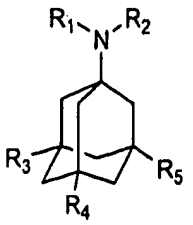
R_1, R_2, R_3, R_4, and R_5 do not all represent hydrogen simultaneously,

or a pharmaceutically-acceptable salt thereof.

21. (New) The method of claim 20, wherein said adamantane derivative is memantine.

22. (New) The method of claim 20, wherein said effective amount is from about 0.01 to 100 mg/kg.

23. (New) A method for blocking the NMDA receptor in a patient diagnosed with Alzheimer's disease and in need of such treatment, comprising orally administering to said patient an effective amount of an adamantane derivative of the general formula



wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1-C_6 alkyl group; and

wherein

R_1, R_2, R_3, R_4, and R_5 do not all represent hydrogen simultaneously,

or a pharmaceutically-acceptable salt thereof.

24. (New) The method of claim 23, wherein said adamantane derivative is memantine.

25. (New) The method of claim 23, wherein said effective amount is from about 0.01 to 100 mg/kg.

REMARKS

I. Status of Claims

Claims 1-25 are pending in this reexamination.

Claim 1 has been amended to recite oral administration of an adamantane derivative to a patient diagnosed with Alzheimer's disease.

New claims 14-25 have been added to recite: the treatment of cerebral ischemia (claim 14) comprising administration of memantine (claim 15) in an effective amount of about 0.01 to 100 mg/kg (claim 16); the treatment of an imbalance of neuronal stimulation after Alzheimer's disease (claim 17) comprising administration of memantine (claim 18) in an effective amount of about 0.01 to 100 mg/kg (claim 19); a method for blocking an excessive influx of calcium through NMDA receptor channels (claim 20) comprising administration of memantine (claim 21) in an effective amount of about 0.01 to 100 mg/kg (claim 22); and a method for blocking the NMDA receptor (claim 23) comprising administration of memantine (claim 24) in an effective amount of about 0.01 to 100 mg/kg (claim 25).

Claims 4, 5, 7, and 9 are patentable and/or confirmed.

Claims 1-3, 6, 8, and 10-13 have been rejected under 35 U.S.C. § 102(b).

II. Claim Support

Support for the amendment to claim 1 is found in the specification at, for example, col. 4, lines 40-43 and col. 8, lines 10-45 (Examples 3 and 4), which disclose the use of oral dosage forms (i.e., "tablets" and "coated tablets"); and col. 3, lines 7-16 and claim 10, which disclose administration to a patient diagnosed with Alzheimer's disease.

Support for new claims 14-16 is found in the specification at, for example, col. 3, lines 7-16 and 23-24; col. 4, lines 38-43; col. 8, lines 10-45; and in original claims 1 and 10.

Support for new claims 17-19 is found in the specification at, for example, col. 2, lines 46-51; col. 3, lines 7-16 and 23-24; col. 4, lines 38-43; col. 8, lines 10-45; and in original claims 1 and 10.

Support for new claims 20-22 is found in the specification at, for example, col. 2, lines 46-51; col. 3, lines 7-16 and 23-24; col. 4, lines 38-43; col. 8, lines 10-45; and in original claims 1 and 10.

Support for new claims 23-25 is found in the specification at, for example, col. 3, lines 7-16 and 23-24; col. 4, lines 38-43; col. 5, lines 41-43; col. 6, line 68 to col. 7, line 2; col. 8, lines 10-45; and in original claims 1 and 10.

No new matter has been added, and the scope of the claims has not been enlarged.

III. Introductory Comments

The present invention relates to the discovery that certain adamantane derivatives (especially memantine) can be used to treat patients diagnosed with Alzheimer's disease. Despite decades of intense research, as of May 2005 only five drugs have been approved by the Food and Drug Administration (FDA) for the treatment of Alzheimer's disease patients: tacrine (Cognex®), approved in 1993; donepezil (Aricept®), approved in 1996; rivastigmine (Exelon®), approved in 2000; galantamine (Reminyl®, now called Razadyne™), approved in 2001; and memantine (Namenda®), approved in 2003. Not one of these drugs was available in 1989, and tacrine is no longer marketed in the United States because of its liver toxicity. Memantine (a preferred embodiment of the present invention) is approved for treatment of moderate to severe Alzheimer's disease, whereas all of the others have only been approved for mild to moderate Alzheimer's disease. Additionally, memantine is the only one that does not act as a cholinesterase inhibitor.

In his accompanying declaration, Dr. Howard Fillit (a practicing geriatrician and neurobiologist with more than 25 years experience in treating Alzheimer's disease patients) describes why the use of memantine for treating patients diagnosed with Alzheimer's disease was a surprising discovery. *See* accompanying Declaration of Howard Fillit, M.D. ("Fillit Declaration"). In another accompanying declaration, Dr. Myron Weiner (a practicing psychiatrist with more than 20 years experience in treating Alzheimer's disease patients) describes the struggle to develop effective treatments for Alzheimer's disease, as well as the significant and surprising discovery that memantine could effectively treat patients diagnosed with this disease. *See* accompanying Declaration of Myron Weiner, M.D. ("Weiner Declaration").

The invention defined by the present claims is not anticipated by the prior art and was a surprise at the time the invention was made. Drs. Weiner and Fillit conclude that memantine (a preferred embodiment of the present invention) provides surprising and unexpected benefits for at least three reasons. First, in 1989 (the earliest year to which the '703 patent is entitled to a claim of priority), memantine was contraindicated for "severe confusional states," which included Alzheimer's disease patients; and memantine was reported to cause "agitation" as a side effect, a symptom frequently experienced by Alzheimer's disease patients. *See* Rote Liste, 63 008 (1986). Dr. Weiner reports that those of ordinary skill would therefore not have expected memantine to be effective for the treatment of Alzheimer's disease patients because administration of memantine could have worsened the condition of these particular patients. *See* Weiner Declaration at ¶¶ 18-20.

Second, memantine was commonly believed to be a dopaminergic agent in 1989. At that time, the prevailing theory of Alzheimer's disease treatment focused on the cholinergic system, and dopaminergic agents were thought to promote psychosis. Dr. Weiner states that those of ordinary skill would not have considered administering memantine to treat Alzheimer's disease patients in

1989 because this compound was unrelated to the cholinergic theory of treatment and could have aggravated the condition of an Alzheimer's disease patient by causing undesirable behavioral effects. *See* Weiner Declaration at ¶¶ 21-23.

Third, by 1989, the only published study involving the administration of memantine to Alzheimer's disease patients plainly concluded that memantine is not effective for the treatment of Alzheimer's disease. *See* Fleischhacker at p. 89. As set forth in the accompanying Fillit declaration and for at least the foregoing reasons, those of ordinary skill in the art would have found it surprising and unexpected that memantine could be effectively used to treat patients diagnosed with Alzheimer's disease in 1989, and would have had no reasonable expectation that memantine could be successfully used in this manner. *See* Fillit Declaration at ¶¶ 29-32.

IV. Rejections Under 35 U.S.C. § 102(b)

Claims 1-3, 6, 8, and 10-13 have been rejected under 35 U.S.C. § 102(b) as anticipated by Rote Liste, 63 008 (1986) ("the Rote Liste"); Marcea et al., *Therapiewoche*, 38:3097-3100 (1988) ("Marcea"); Ambrozi et al., *Pharmacopsychiatry*, 21:144-146 (1988) ("Ambrozi"); and Fleischhacker et al., *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 10:87-93 (1986) ("Fleischhacker").

Amended claim 1 is directed to the prevention or treatment of cerebral ischemia in a patient diagnosed with Alzheimer's disease. As defined in the '703 patent, "cerebral ischemia" refers to an imbalance of neuronal stimulation in which an excessive influx of calcium through NMDA receptor channels leads to degeneration and loss of brain cells (col. 2, lines 46-51). This imbalance can be initiated by various conditions, including Alzheimer's disease (col. 3, lines 10-16), and is characterized by a substantial increase in excitatory amino acids, which allows for an excessive influx of calcium through NMDA receptor channels leading to loss of brain cells (col. 2, lines 46-

52). By blocking the NMDA receptor, certain adamantane derivatives (especially memantine) prevent this excessive calcium influx, thereby reducing subsequent neuronal death. Thus, memantine treats patients diagnosed with Alzheimer's disease by alleviating the neurodegenerative consequences of an imbalance of neuronal stimulation (col. 3, lines 7-10). *See* Weiner Declaration at ¶ 16.

A. **Rote Liste**

The Rote Liste, published in 1986, discloses that memantine may be used for the following indications:

> Cerebral and spinal spasms, organic brain syndrome, cerebrovascular insufficiency, disorders which require enhancement of vigilance, such as comatose states. Parkinson's syndrome.

The Rote Liste does not disclose the administration of memantine to a patient "diagnosed with Alzheimer's disease," as required by amended claim 1. Accordingly, the anticipation rejection over the Rote Liste should be withdrawn. Further, the Rote Liste does not inherently disclose the administration of memantine to a patient "diagnosed with Alzheimer's disease." To establish inherency, a reference "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (citing *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991)).

Here, the Rote Liste does not inherently anticipate the present claims because patients suffering from the conditions listed in this reference are not "necessarily" patients diagnosed with Alzheimer's disease. For example, patients with "organic brain syndrome" (OBS) do not necessarily include patients diagnosed with Alzheimer's disease. OBS is a non-specific term that was used in the 1980s to describe a patient who was generally confused. Typical characteristics of

OBS include impairment of memory, ability to concentrate, thinking, understanding, orientation, and affectivity. Fillit Declaration at ¶¶ 10-11. Not all patients afflicted with, e.g., an impaired ability to concentrate, are afflicted with Alzheimer's disease. *Id.*

Patients with OBS could have been suffering from various conditions, such as delirium (an acute form of confusion) or anemia, in which an anemic patient's low blood count would have made him/her appear tired and inattentive, corresponding to an OBS clinical state. Fillit Declaration at ¶ 10. OBS could have also described patients suffering from chronic or acute forms of dementia, which in turn could have been caused by any number of other disorders. *Id.* at ¶ 11. For instance, thyroid problems, vitamin B12 deficiency, depression, vascular dementia, Parkinson's disease, or drug abuse could lead to symptoms of dementia. *Id.* Further, all of these different dementias would have fallen within the scope of the term OBS. *Id.* A syndromal description of OBS would have revealed nothing about the underlying condition causing the OBS clinical state. *Id.*

Therefore, treatment of patients diagnosed with OBS does not necessarily include patients diagnosed with Alzheimer's disease, or any other illness, in particular. Similarly, none of the other conditions enumerated in the Rote Liste inherently describes Alzheimer's disease patients either. With the sole exception of Parkinson's syndrome, which is not Alzheimer's disease, all of the other enumerated conditions are non-specific syndromes that could be present in patients suffering from a wide range of disorders unrelated to Alzheimer's disease (e.g., comatose states). Fillit Declaration at ¶ 12. Memantine is not "necessarily" indicated for patients diagnosed with Alzheimer's disease, based on the Rote Liste. Accordingly, treatment of patients diagnosed with Alzheimer's disease, as required by claim 1, is not inherent in this reference.

In view of the foregoing, claims 1-3, 6, 8, and 10-25 are not anticipated by the Rote Liste,

either expressly or inherently. Therefore, this rejection should be withdrawn.

B. Marcea

Marcea does not disclose administering memantine to a patient "diagnosed with Alzheimer's disease," as required by amended claim 1. Accordingly, the anticipation rejection over Marcea should be withdrawn. Further, Marcea does not inherently disclose the administration of memantine to a patient "diagnosed with Alzheimer's disease" because the patient population described in this reference does not "necessarily" include Alzheimer's disease patients.

Marcea discloses a study of two treatment groups of 30 patients each: a memantine treatment group and a dh-ergotoxin treatment group. Marcea (German) at p. 3097; Marcea (English Translation) at p. 2, lines 3-7. The Marcea patient population is described as inpatients with moderately severe symptoms of cerebro-organic psycho-syndrome, determined based on ICD.9 criteria, "(No. 290.0, 290.1, 290.4)." Marcea (German) at p. 3098; Marcea (English Translation) at p. 2, lines 3-5. "Cerebro-organic psycho-syndrome" is a synonym for OBS and has been used by those of ordinary skill in the art in the same manner as OBS since the 1980s. *See* Fillit Declaration at ¶ 14. For convenience, the abbreviation "OBS" will be used herein to refer to cerebro-organic psycho-syndrome.

Marcea does not indicate that any of the patients in this study were diagnosed with Alzheimer's disease. Further, the ICD-9 codes 290.0, 290.1, and 290.4 cited in Marcea do not necessarily include Alzheimer's disease patients. Fillit Declaration at ¶¶ 15-21. In 1989, only one of these codes mentioned Alzheimer's disease. Specifically, ICD-9 No. 290.1 referred to "presenile dementia," which included "brain syndrome with presenile brain disease" and dementia in: Alzheimer's disease, Jakob-Creutzfeldt disease, and Pick's disease of the brain, each of which was classified under an additional, separate diagnostic code (e.g., ICD-9 No. 331.0 for

Alzheimer's disease). *Id.* Thus, patients classified under ICD-9 No. 290.1 did not "necessarily" have Alzheimer's disease.

Further, Marcea does not disclose that patients generally classified under ICD-9 No. 290.1 were necessarily included in the study. Since the reference simply lists the three ICD-9 codes as "290.0, 290.1, 290.4," there is no way of knowing how many, if any, patients were included within each diagnostic classification. Fillit Declaration at ¶ 17. Thus, patients classified under ICD-9 No. 290.1, let alone Alzheimer's disease patients, were not "necessarily" included in the Marcea study. *Id.*

Marcea also fails to disclose what conditions afflicted the patients in each treatment group. Specifically, there is no disclosure in Marcea to suggest that patients classifed under ICD-9 No. 290.1, let alone Alzheimer's disease patients, were included in the memantine treatment group rather than the dh-ergotoxin treatment group. And even if Alzheimer's disease patients were included in both the study and the memantine group, a person of ordinary skill in the art still would not have known whether any such patients actually benefited from the administration of memantine because Marcea does not indicate which patients benefited from memantine treatment. Fillit Declaration at ¶ 18. In summary, the Marcea disclosure would not have been enough to suggest to those of ordinary skill in 1989 that patients diagnosed with Alzheimer's disease were "necessarily" included in this study or that there would have been a reasonable expectation of success regarding the use of memantine to treat Alzheimer's disease patients. *See id.* at ¶ 21.

In view of the foregoing, claims 1-3, 6, 8, and 10-25 are not anticipated by Marcea, either expressly or inherently. Therefore, this rejection should be withdrawn.

C. **Ambrozi**

Ambrozi does not disclose administering memantine to a patient "diagnosed with Alzheimer's disease," as required by amended claim 1. Accordingly, the anticipation rejection over Ambrozi should be withdrawn. Further, Ambrozi does not inherently disclose the administration of memantine to a patient "diagnosed with Alzheimer's disease" because the patient population described in this reference does not "necessarily" include Alzheimer's disease patients.

Ambrozi discloses a study of the administration of memantine or placebo to geriatric patients suffering from severe chronic diseases of the central nervous system. Ambrozi does not identify any patients as having been diagnosed with Alzheimer's disease. Furthermore, the symptoms described in the Ambrozi article could encompass patients suffering from a range of medical conditions unrelated to Alzheimer's disease (e.g., schizophrenia, stroke, Parkinson's Disease, and multiple sclerosis). Fillit Declaration at ¶ 22. Ambrozi also discloses concomitant diseases that were present in the patient population, co-medications administered to the patients, and patient exclusion criteria, but these descriptions do not identify the particular diseases that afflicted the patients in the Ambrozi study, let alone the patients included in the memantine treatment group. *Id.* at ¶ 23. Thus, the patient population described in Ambrozi does not "necessarily" include Alzheimer's disease patients.

Further, Ambrozi concludes that memantine is "suitable for the treatment of the organic psychosyndrome ... or impaired cerebral function ... or dementia as one category of organic mental disorders (DSM-III)." Ambrozi at p. 146. None of these conditions necessarily includes Alzheimer's disease patients. Organic psychosyndrome (another term for OBS) and impaired cerebral function are non-specific terms that could describe a variety of illnesses. Fillit Declaration at ¶ 26. Additionally, according to DSM-III, organic mental disorders were grouped into three

categories in 1989, only the first of which mentioned Alzheimer's disease. *Id.* at ¶ 27. Specifically, the first category included primary degenerative dementia of the Alzheimer type and multi-infarct dementia. *Id.* Thus, patients suffering from dementia as one category of organic mental disorders (DSM-III), were not "necessarily" diagnosed with Alzheimer's disease.

Nevertheless, even if Alzheimer's disease patients were included in the Ambrozi study, and even if some of those patients were in the memantine treatment group, a person of ordinary skill in the art still could not have known whether any such patients actually benefited from the administration of memantine because Ambrozi provides no information on the change in status of any Alzheimer's disease patients and does not identify what disorders afflicted the patients who showed improvement from memantine treatment. Fillit Declaration at ¶ 24. In summary, the Ambrozi disclosure would not have been enough to suggest to those of ordinary skill in 1989 that patients diagnosed with Alzheimer's disease were "necessarily" included in the study or that there would have been a reasonable expectation of success regarding the use of memantine to treat Alzheimer's disease patients. *See id.* at ¶ 28.

In view of the foregoing, patients diagnosed with Alzheimer's disease were not "necessarily" included in the Ambrozi study. Therefore, claims 1-3, 6, 8, and 10-25 are not anticipated by Ambrozi, either expressly or inherently, and this rejection should be withdrawn.

D. Fleischhacker

Fleischhacker discloses a study of 20 patients said to be diagnosed with senile dementia of the Alzheimer type (SDAT). According to Fleischhacker, "10 patients received 10-30 mg Memantine *pro die* [(i.e., per day)] intravenously." Fleischhacker at p. 87 (emphasis added).

Amended claim 1 and new claims 14-21 recite oral administration of the claimed compounds. Fleischhacker discloses only intravenous administration, and does not disclose or

suggest any alternative routes of administration. Therefore, claims 1-3, 6, 8, and 10-23 are not anticipated by Fleischhacker, and this rejection should be withdrawn.

Additionally, the Examiner asserts that Fleischhacker "states memantine has a beneficial effect in patient (sic) with SDAT with increased drive and awakeness (see page 88)." Office Action at p. 3. On the contrary, Fleischhacker expressly states that the "study showed no statistically calculable proof for the superiority of Memantine over placebo in patients suffering from SDAT." Fleischhacker at p. 89, *Discussion*. The Examiner appears to be referencing the disclosure on page 88 of Fleischhacker, which states:

> Memantine showed less side effects and a more significant increase of drive in a study comparing it to Amantadine (Fischer et al. 1977). The aim of the study presented in the following is to evaluate whether Memantine has a beneficial effect in patients with SDAT.

The 1977 Fischer study involved patients with Parkinson's disease, not Alzheimer's disease. *See* Fischer et al., *Arzneimittelforschung*, 27(7):1487-1489 (1977) (abstract enclosed). Further, there is no disclosure in Fleischhacker that teaches or suggests that any beneficial effects of memantine have been demonstrated in Alzheimer's disease patients. *See* Fillit Declaration at ¶¶ 29-31. Rather, that was the objective of the Fleischhacker study - an objective that was not met. Thus, if anything, Fleischhacker teaches away from the use of memantine for treating patients diagnosed with Alzheimer's disease. Thus, this ground for rejection should also be withdrawn.

V. New Claims 14-25

Each of new claims 14-25 is narrower than the original claims because the features of "orally" administering an adamantane derivative (claims 14-25), administering an adamantane derivative to a patient "diagnosed with Alzheimer's disease" (claims 14-25), "treatment" only (claims 14-19), treatment of an "imbalance of neuronal stimulation after Alzheimer's disease"

(claims 17-19), "blocking an excessive influx of calcium through NMDA receptor channels" (claims 20-22), and "blocking the NMDA receptor" (claims 23-25) did not appear in the original claims.

Additionally, each of new claims 14-25 is patentable over the prior art because all of these claims require the step of "orally" administering an adamantane derivative to a patient "diagnosed with Alzheimer's disease." The Rote Liste, Marcea, and Ambrozi publications each fails to suggest or disclose, either expressly or inherently, the administration of memantine to a patient "diagnosed with Alzheimer's disease;" and Fleischhacker fails to disclose "orally" administering.

Furthermore, not one of the Rote Liste, Marcea, Ambrozi, or Fleischhacker publications discloses or suggests the treatment of "cerebral ischemia" (claims 14-16), the treatment of an "imbalance of neuronal stimulation after Alzheimer's disease" (claims 17-19), "blocking an excessive influx of calcium through NMDA receptor channels" (claims 20-22), or "blocking the NMDA receptor" (claims 23-25), as called for in the present claims.

VI. November 24, 2004 and December 6, 2004 Information Disclosure Statements

To date, the patentee has not received the initialed lists of references (PTO/SB/08 forms) for the Information Disclosure Statements filed November 24, 2004 and December 6, 2004. A copy of the PTO/SB/08 forms filed on each of these dates is enclosed. In accordance with MPEP §§ 609 and 707.05(b), it is requested that each reference listed on these forms be given thorough consideration and be cited of record in the prosecution history of the present reexamination proceeding by the Examiner initialing these forms. The patentee also requests that a copy of the initialed forms be sent with the Examiner's next communication.

VII. Conclusion

In view of the foregoing, the pending claims are believed to be patentable over the prior art and issuance of a certificate of reexamination for all pending claims is respectfully requested.

Dated: May 9, 2005

Respectfully submitted,

By: _____
S. Peter Ludwig
Reg. No. 25,351
Attorney for Patentee

Darby & Darby P.C.
Post Office Box 5257
New York, NY 10150-5257
212-527-7700
212-527-7701 (Fax)

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Reexamination of: U.S. Patent No. 5,061,703
Of Joachim BORMANN, Markus GOLD, and Wolfgang SCHATTON

Control No: 90/007,176

Examiner: Kevin E. Weddington

Confirmation No.: 5288

Art Unit: 1614

Filed: August 18, 2004

Title: ADAMANTANE DERIVATIVES IN THE PREVENTION AND TREATMENT OF CEREBRAL ISCHEMIA

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT PURSUANT TO 37 C.F.R. §§ 1.116 AND 1.530

Sir:

In response to the Office Action mailed August 16, 2005, and pursuant to 37 C.F.R. §§ 1.530(d)-(j), please amend the claims of U.S. Patent No. 5,061,703 ("the '703 patent") as follows:

IN THE CLAIMS:

Please amend claim 10 as follows:

10. (Amended) A method according to claim 1 for the treatment of Alzheimer's disease, wherein said adamantane derivative is memantine and said effective amount is from about 0.01 to 100 mg/kg.

Please cancel claims 20-25.

REMARKS

I. Status of Claims

Claims 1-25 are pending in this reexamination.

Claims 1-9 and 11-19 are patentable and/or confirmed.

Claim 10 has been rejected under 35 U.S.C. § 112, second paragraph.

Claims 20-25 have been rejected under 35 U.S.C. § 305.

Claim 10 has been amended to specify the administration of memantine and its effective amount.

Claims 20-25 have been canceled.

II. Claim Support

Support for the amendment to claim 10 is found in the specification at, for example, col. 3, line 23, which discloses 1-amino-3,5-dimethyl adamantane, and col. 4, lines 38-40, which specifies the suitable dosing range.

No new matter has been added, and the scope of the claims has not been enlarged.

III. Examiner Interview Summary Statement Under 37 C.F.R. 1.560(b)

The Examiner is thanked for all courtesies extended to the patentee's attorney, S. Peter Ludwig, during the telephone interview held September 26, 2005. During the interview, counsel for the patentee indicated that the patentee would cancel claims 20-25 and requested amendment of claim 10 (to specify the administration of memantine and its effective amount) to overcome the rejection under 35 U.S.C. § 112. The support for the claim amendment in the specification (set forth above) was discussed with the Examiner. The Examiner agreed that canceling claims 20-25

and amending claim 10 to specify the administration of memantine and its effective amount would overcome the rejection of claim 10 under 35 U.S.C. § 112, and moot the rejection of claims 20-25 under 35 U.S.C. § 305. Based on the September 26, 2005 interview, these amendments are believed to place the remaining claims in condition for allowance and for issuance of a Certificate of Reexamination.

IV. Conclusion

In view of the foregoing, the subsisting claims in this reexamination proceeding are believed to be in condition for allowance, and issuance of a Certificate of Reexamination for claims 1-19 is respectfully requested.

Dated: October 17, 2005

Respectfully submitted,

By: _____

S. Peter Ludwig
Reg. No. 25,351
Attorney for Patentee

Darby & Darby P.C.
Post Office Box 5257
New York, NY 10150-5257
212-527-7700
212-527-7701 (Fax)